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BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 2004D-0524
Comment on Draft Guidance Document

Dear Sir or Madam:

The undersigned, on behalf of GlaxoSmithKline (GSK), submits the following comment on the Food and Drug Administration's (FDA's) recent Draft Guidance for Industry: *ANDAs: Pharmaceutical Solid Polymorphism; Chemistry, Manufacturing, and Controls Information* (Dec. 2004) (Draft Guidance). *See* 69 FR 75987 (Dec. 20, 2004).

The Draft Guidance proposes a "framework for making regulatory decisions on drug substance sameness" for drugs that exist in polymorphic forms. *Id.* at 75988. It also includes a series of "decision trees" to advise generic drug sponsors when such forms must be monitored and carefully controlled. *Id.* The Draft Guidance, when finalized, will represent FDA's "current thinking" on the subject of polymorphism. *Id.*

GSK welcomes the agency's attempt to clarify standards with respect to polymorphism. As FDA acknowledges in the Draft Guidance, polymorphism may impact the physical or chemical properties of a drug substance, including "melting point, chemical reactivity, apparent solubility, dissolution rate, optical and mechanical properties, vapor pressure, and density." Draft Guidance at lines 74-75 (footnote omitted). These properties may affect the "stability, dissolution, and bioavailability" – and thus the "quality, safety, and efficacy" – of a drug product. *Id.* at lines 77-78.

GSK is concerned, however, about several statements in the Draft Guidance, including those regarding the standards for identity in compendial monographs issued by the United States Pharmacopeia (USP). In addition, the

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Draft Guidance fails to address the impact that polymorphism may have on topical drug products. For these reasons, and as discussed below, GSK respectfully requests that FDA amend the Draft Guidance as follows:

1. **The Statement That Polymorphism Cannot Render Drug Substances Different Active Ingredients Should Be Revised**

The Draft Guidance states that "differences in drug substance polymorphic forms do not render drug substances different active ingredients for the purposes of ANDA approvals within the meaning of the [Food, Drug, and Cosmetic] Act and FDA regulations." Draft Guidance at lines 190-92. According to the Draft Guidance, this statement is supported by, and consistent with, the preamble to FDA's original ANDA regulations. *See id.* at lines 185-90. There, the agency rejected a blanket proposal that would have required complete physical and chemical identity between generic and reference drug products. *See id.* at line 186; *see also* 57 FR 17950, 17958 (Apr. 28, 1992).

The preamble is far more qualified, however, than the Draft Guidance suggests. It makes clear that polymorphism may well render drug substances different active ingredients:

> Under the statute, an ANDA applicant must show that its active ingredient is the same as that in the reference listed drug (21 USC 355(j)(2)(A)(ii)). FDA will consider an active ingredient to be the same as that of the reference listed drug if it meets the same standards for identity. In most cases, these standards are described in the [USP]. *However, in some cases, FDA may prescribe additional standards that are material to the ingredient's sameness. For example, for some drug products, standards for crystalline structure or stereoisomeric mixture may be required.*

57 FR at 17959 (emphasis added).

This passage, omitted from the Draft Guidance, indicates that polymorphism can be material to the issue of drug substance sameness. GSK therefore recommends that lines 190-92 either be removed from the Draft Guidance, or be revised to fully reflect FDA's longstanding views regarding polymorphism. Any final guidance document should also outline the factors that FDA will consider in determining when it will go about prescribing "additional standards" that are material to sameness. *Id.*

2. The Statement That Standards For Identity Refer Only To The Definition Sections Of USP Monographs Should Be Removed

The Draft Guidance states that "[w]hen a [USP] monograph exists for a particular drug substance, standards for identity generally refer to the *definition* (i.e. chemical name, empirical formula, molecular structure, description) at the beginning of the monograph." Draft Guidance at lines 179-81 (emphasis added).

This statement appears to conflict with FDA's prior statements regarding USP monographs. The agency has stated in the past that standards for identity include all relevant tests and specifications in monographs. One example is FDA's response to a citizen petition regarding GSK's Ceftin® (cefuroxime axetil). *See* Citizen Petition Response, Docket Nos. 00P-1550, 01P-0428 (Feb. 15, 2002) (Ceftin® Response). There, after discussing the same preamble language cited in the Draft Guidance, the agency stated:

> Therefore, if an ANDA applicant provides sufficient information to show that the cefuroxime axetil (in wholly or partially crystalline form) in its proposed generic cefuroxime axetil drug product meets the standards for identity in the *USP*, FDA will consider the proposed generic drug product to contain the "same" active ingredients as the reference listed drug, Ceftin. *The standards for identity with respect to cefuroxime axetil include test/specifications relating to identification, crystallinity, diastereoisomer ratio, and assay.*

Id. at 9 (emphasis added); *see id.* at 8-9.[1]

Perhaps more importantly, the Draft Guidance appears to conflict with the USP's own policy regarding the standards for identity in its monographs. The 28th revision of the USP states throughout its *Preface* and *General Notices* that the standards for identity of compendial drug substances include all of the relevant tests and specifications in the monographs. For example:

- "The *identity* of an official article, as expressed by its name, is established if it *conforms in all respects* to the requirements of its

[1] In the Ceftin® case, GSK argued that FDA should not approve a cefuroxime axetil product in which the active ingredient was in crystalline form, because it would not comply with the USP monograph. That monograph was then amended to recognize the crystalline form. Thus, FDA determined that "[t]he need to address this issue was obviated . . . ." Ceftin® Response at 6. The portions of the monograph that changed, however, were not in the definition section; they were in the *body* of the monograph.

monograph and other relevant portions of the compendia (e.g., *General Notices*)."

- "Unless specifically exempted elsewhere in this Pharmacopeia, the *identity*, strength, quality, and purity of an official article are determined by the *definition, physical properties, tests, assays, and other specifications* relating to the article, whether incorporated in the monograph itself, in the *General Notices*, or in the section *General Chapters*."

- *"Assay and test procedures* are provided for determining compliance with the Pharmacopeial *standards of identity*, strength, quality, and purity."

- "Every compendial article in commerce shall be so constituted that when examined in accordance with these *assay and test procedures*, it *meets all the requirements* in the monograph defining it."

- "The Pharmacopeial *tests* headed *Identification* are provided as an aid in verifying the *identity* of articles as they are purported to be, such as those taken from labeled containers. . . . *Other tests and specifications* in the monograph often contribute to establishing or confirming the *identity* of the article under examination."

USP 28/NF 23 (2005) at xi, 6, 7, 7, 8 (emphasis added).

For these reasons, GSK recommends that FDA remove lines 179-81 from the Draft Guidance. Any final guidance document should make clear that, consistent with USP policy, the relevant standards for identity of compendial drug substances are contained within all relevant sections of the USP monographs. The guidance should also articulate how FDA will establish public standards of identity – including standards with respect to polymorphism – in the absence of compendial monographs.

3. The Draft Guidance Should Address The Impact That Polymorphism May Have on Topical Drug Products

The Draft Guidance discusses polymorphism primarily in the context of solid oral drug products. For example, the Draft Guidance states that whether bioavailability may be affected by polymorphism is determined by the factors that govern drug absorption, including "gastrointestinal motility" and "intestinal permeability." Draft Guidance at lines 104-05. It also states that the effect of

polymorphism may depend on whether a drug product is manufactured through "direct compression" or "wet granulation." *Id.* at lines 133-36.

These factors, however, do not address the potential impact that polymorphism may have on the stability, dissolution, and bioavailability of topical drug products. For example, the melting point of a drug can influence the rate of that drug's passage from a topical formulation onto and through skin. *See* Jane Shaw, *Development of Transdermal Therapeutic Systems: Drug Development and Industrial Pharmacy*, Vol. 9 (4), at 579-603 (1983). Thus, melting point can have a significant effect on the bioavailability and, by association, the safety and efficacy of a topical product.

It is also well known that polymorphic forms may undergo phase conversion over time. This is particularly true in the presence of moisture, which can cause amorphous forms to crystallize at lower temperatures. *See* Michael J. Pikal, "Impact of Polymorphism on the Quality of Lyophilized Products," in *Polymorphism in Pharmaceutical Solids: Drugs and the Pharmaceutical Sciences*, Vol. 95, at 408 (Marcel Dekker, Inc., 1999).

The Draft Guidance acknowledges that the presence of moisture can lead to phase conversion, and that this can affect the bioavailability of the drug product. *See* Draft Guidance at lines 145-51. It then states that this "generally is not of serious concern," provided that the conversion occurs consistently, as a part of a validated manufacturing process where bioequivalence has been demonstrated. *Id.* at lines 148-51.

In topical drug products, however, phase conversion does not occur consistently during manufacturing, but rather inconsistently during manufacturing, use, or storage of the product. Dosage forms such as creams and lotions typically contain significant aqueous components, and may absorb additional moisture over time from product packaging or from the environment. This increasing moisture may have a significant impact, leading to sudden and unpredictable crystallization of the drug substance. *See* Michael J. Pikal, "Freeze Drying," in *Encyclopedia of Pharmaceutical Technology*, Vol. 2, at 1312 (James S. Swarbrick & James C. Boylan, eds. 2002). These issues should be addressed in the guidance document, or FDA should make clear that the guidance applies only to solid oral drug products.

Last, the Draft Guidance places undue reliance on the idea that significant differences in the bioavailability of polymorphic forms will be detected in bioequivalence studies. *See, e.g.*, Draft Guidance at lines 194-96. The requirements that generic drug products be bioequivalent to, and contain the same active ingredients as, reference drug products are separate requirements that should not

be conflated. *See* 21 USC 355(j)(2)(A)(ii), (iv). In the case of topical drug products, in particular, the agency's bioequivalence methodology is not sensitive enough to detect potentially significant differences in bioavailability. *See* 21 CFR 320.24(b)(4).

III. Conclusion

GSK appreciates the agency's effort to clarify standards with respect to the difficult subject of polymorphism. GSK believes, however, that several aspects of the draft document are inconsistent with longstanding FDA or USP policy, and respectfully requests that the Draft Guidance be revised as discussed above.

Thank you for your consideration.

Patrick J Crowley

Patrick J. Crowley
Vice President
Pharmaceutical Development

cc: Docket No. 2004P-0290
Docket No. 2004P-0488
David J. Cummings, Ph.D.